Non-Targeted Effects and the Dose Response for Heavy Ion Tumorigenesis

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BACKGROUND

There is no human epidemiology data available to estimate the heavy ion cancer risks experienced by astronauts in space. Studies of tumor induction in mice are a necessary step to estimate risks to astronauts. Previous experimental data can be better utilized to model dose response for heavy ion tumorigenesis and plan future low dose studies.

DOSE RESPONSE MODELS

The Harderian Gland data of Alpen et al.[1-3] was re-analyzed [4] using non-linear least square regression. The data set measured the induction of Harderian gland tumors in mice by high-energy protons, helium, neon, iron, niobium and lanthanum with LET's ranging from 0.4 to 950 keV/micron. We were able to strengthen the individual ion models by combining data for all ions into a model that relates both radiation dose and LET for the ion to tumor prevalence. We compared models based on Targeted Effects (TE) to one motivated by Non-targeted Effects (NTE) that included a bystander term that increased tumor induction at low doses non-linearly. Using several model ranking criteria, the non-linear NTE models fit the combined data better than the TE models that are linear at low doses. We evaluated the differences in the relative biological effectiveness (RBE) and found the NTE model provides a higher RBE at low dose compared to the TE model.

POWER ANALYSIS

The final NTE model estimates were used to simulate example data to consider the design of new experiments to detect NTE at low dose for validation. Power and sample sizes were calculated for a variety of radiation qualities including some not considered in the Harderian Gland data set and with different background tumor incidences. We considered different experimental designs with varying number of doses and varying low doses dependant on the LET of the radiation. The optimal design to detect a NTE for an individual ion had 4 doses equally spaced below a maximal dose where "bending" due to cell sterilization was < 2%. For example at 100 keV/micron we would irradiate at 0.03 Gy, 0.065 Gy, 0.13 Gy, and 0.26 Gy and require 850 mice including a control dose for a sensitivity to detect NTE with 80% power. Sample sizes could be improved by combining ions similar to the methods used with the Harderian Gland data.

REFERENCES

[1] Fry R.J.M. et al (1985) *Radiat. Res.* 104: S188–195. [2] Alpen E.L. et al (1993) *Radiat. Res.* 88: 132–143. [3] Alpen E.L. et al (1994) *Adv. Space Res.* 14: 573–581, [4] Cucinotta F.A. and Chappell, L.J. (2010) *Mut. Res.(online)*.